CHRONIC PARKINSONISM SECONDARY TO INTRANASAL ADMINISTRATION OF A PRODUCT OF MEPERIDINE-ANALOGUE SYNTHESIS

To the Editor: We wish to report another case of parkinsonism associated with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP).[1-3] A previously healthy 25-year-old man was admitted to another hospital in an immobile, mute state. His girlfriend stated that over eight days he had gradually become withdrawn and had stopped talking and eating. He had a long history of drug abuse. Routine laboratory examination of the cerebrospinal fluid, a CT head scan, and an electroencephalogram were normal. The patient was diagnosed as having an acute psychotic state with catatonia, and he was treated with haloperidol in a psychiatric facility.

He did not improve appreciably, and 11 months later he was admitted to our hospital for neurologic assessment. He had severe bradykinesia; he walked with a stooped, shuffling gait, drooled excessively, spoke in a monosyllabic whisper, and required assistance to feed himself. There was no family history of parkinsonism. A diagnosis was made of severe parkinsonism of unknown cause.

The patient was started on levodopa and carbidopa and responded dramatically. He was ecstatic; for the first time in a year he was able to speak clearly and to feed himself. He said it was "like getting out of a cage." He described "snorting" a home-synthesized meperidine analogue daily for seven days before his illness. He had made and taken this compound many times previously without mishap, but something went wrong with the synthesis of the batch associated with his illness.

According to the patient's method,[4] methylamine hydrochloride, formaldehyde, and α-methylstyrene were reacted to form the intermediate product 1-methyl-4-phenyl-4-piperidinol. This compound was then reacted with propionic anhydride to form 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP), a potent narcotic. The batch causing the Parkinson's syndrome was brownish, as opposed to the usual white color, and the patient suspected that the discolored, recovered propionic anhydride was the problem. "Wet" propionic anhydride would give dehydration of the piperidinol to form MPTP[4] as a major side reaction. Powder obtained from the patient's home was later identified by gas chromatography–mass spectrometry to be a mixture of MPPP, MPTP, and the piperidinol.

Table 1. Levels of Gamma-Aminobutyric Acid (GABA) and Homovanillic Acid (HVA) in the Patient's Spinal Fluid.

Acid	Control Levels *	Patient's Levels	
		Before Treatment	During Treatment †
		nmol/liter	
GABA[5]	86±42	82	123, 94, 169 ‡
HVA[6]	203±77	55	812, 329, 554

*Means ±S.D.

†The patient was treated with levodopa and carbidopa.

‡This elevation was probably due to inhibition of GABA aminotransferase by hydrazine, a potential metabolite of carbidopa.

The patient did reasonably well during treatment and was able to play a guitar and drive a car. He tended to abuse his levodopa, producing hallucinations and dystonic movements. He also suffered end-of-dose bradykinesia. Concentrations of homovanillic acid and gamma-aminobutyric acid in the cerebrospinal fluid before and after treatment are shown in Table 1. Unfortunately, while attending a party on a wharf 20 months after his original illness, the patient fell into the ocean unnoticed and drowned. An autopsy was performed, but the brain was sectioned perfunctorily without disclosing any gross abnormalities. When we obtained the brain three days later, the substantia nigra had been discarded; no histologic abnormalities were found in the brain regions available for study.

This case is different from previously reported cases[1,2] in that our patient attempted to make MPPP by a different method,[4,7] and he "snorted" the chemical instead of injecting it intravenously. The fact that the MPTP was toxic after intranasal administration is in accord with a recent report of development of parkinsonism in a 37-year-old chemist who had worked with MPTP during eight years.[9] Psychiatrists should be aware of the possibility of this condition in patients presenting with "catatonic schizophrenia," because treatment with antipsychotic medications will worsen the condition of patients with chemically induced Parkinson's disease.

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RECONCILING HUMANE CONCERNS AND LABORATORY ANIMAL RESEARCH

To the Editor: Attempts by various humane societies to secure better federal legislation to improve the welfare of laboratory animals and to reduce the numbers being used have caused intense polarization between them and the biomedical-research establishment. However, there are some common concerns that cannot be ignored. Standards of care for primates, kept in social isolation in cages 0.6 by 0.9 by 1.2 m reflect a Cartesian attitude that ignores the social and emotional variables and correlated physiologic changes that result when group-living, socially dependent monkeys are kept under such impoverished conditions. (These animals often acquire abnormal behaviors, such as self-mutilation, repeated masturbation, rumination, polydipsia, bulimia, and sterotypic movements, which ethologists regard as pathognomonic of frustration and emotional distress.) The validity of research findings derived from animals kept under such conditions is surely to be questioned on scientific as well as humane grounds.

Another potential area of common ground is between those in the biomedical-research field who have expressed concern that there is too much emphasis on treating disease and not enough on preventive medicine and persons (including me) who contend that the primary focus of animal research should be not treatment but prevention of human disease.

Organ transplants, fetal surgery, and vaccines against cancer may soon be commonplace, thanks to animal research, but as our environment becomes increasingly pathogenic, can we regard this as medical progress and can we continue to legitimize the exploitation and suffering of laboratory animals? Certainly, people who are sick should not be denied the best possible treatment, but if greater emphasis were placed on disease prevention, such potentially dan-